



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 901 PCT	<b>FOR FURTHER ACTION</b> See Form PCT/IPEA/416	
International application No. PCT/EP2005/000987	International filing date (day/month/year) 01.02.2005	Priority date (day/month/year) 03.02.2004
International Patent Classification (IPC) or national classification and IPC INV. C07C323/00		
Applicant INDENA S.P.A.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 1 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand  07.11.2005	Date of completion of this report  26.04.2006	
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer  English, R  Telephone No. +31 70 340-2860 	

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

03/03/2005  
14/02/2005  
International application No.  
PCT/EP2005/000987

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4(a))
  - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-12 as originally filed

**Claims, Numbers**

1-6 received on 07.11.2005 with letter of 07.11.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-6
	No: Claims	
Inventive step (IS)	Yes: Claims	1-6
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-6
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

PCT/EP2005/000987

**Re Item V****Reasoned statement with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

Reference is made to the following document:

**D1:** WO 01/68597 A (Indena) 20 September 2001

**1. Subject-matter**

The present application concerns compounds containing two N-deacetylthio-colchicine groups linked together via a cyclic linker group. These compounds have antitumour, antiarthritic, antiinflammatory and antiviral activity.

**2. Novelty**

Document D1 discloses (see examples) compounds containing two N-deacetylthio-colchicine groups linked together via linkers with the formulae  $\text{CO}(\text{CH}_2)_{2-10}\text{CO}$  and  $\text{CONHCH}_2\text{CH}_2\text{CO}$ . Compounds of present claim 1 are not disclosed in D1 or anywhere else in the prior art. Consequently, the subject-matter of claims 1-6 appears to be new and to satisfy the requirements of Article 33(2) PCT.

**3. Inventive step**

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1-6, and discloses compounds containing two N-deacetylthio-colchicine groups linked together via linkers which are not part of the scope of the present invention or are excluded from it and their use in the treatment of tumours and rheumatoid arthritis. These prior-art compounds differ from those of the present application in that the latter have a cyclic group as the linker between the two N-deacetylthio-colchicine groups in place of the acyclic alkylene group of the former.

A comparison of the pharmacological data provided by the applicant shows that the compounds of the present invention in which the linker contains a cyclic group (examples 1-4) show an improved activity (lower  $\text{IC}_{50}$ ) against certain cancers (MCF7, A2780, Widr) compared to one compound of D1 in which the linker is acyclic. The problem to be solved by the present invention may therefore be regarded as the provision of improved compounds for antitumour, antiarthritic, antiinflammatory and antiviral use. The applicant solves this problem by means of the compounds of present claim 1 as demonstrated in the description (table 2).

**INTERNATIONAL PRELIMINARY  
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(SEPARATE SHEET)**

International application No.

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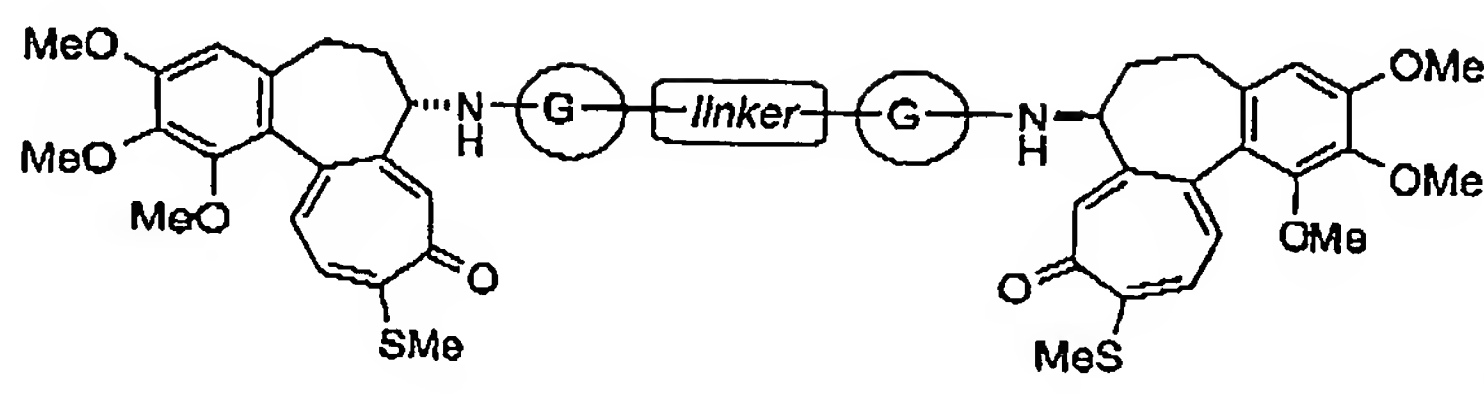
It would not be obvious to the person skilled in the art that replacement of the linker groups of D1 with those of the present application would lead to improved compounds for antitumour, antiarthritic, antiinflammatory and antiviral use. Consequently, the subject-matter of the present claims appears to involve an inventive step and to satisfy the requirements of Article 33(3) PCT.

10/588012

13 JAP20 Rec'd PCT/PTO 01 AUG 2006

**CLAIMS**

## 1. Compounds of formula I



in which:

- the linker is C<sub>3</sub>-C<sub>8</sub> cycloalkyl, a phenylene or C<sub>4</sub>-C<sub>6</sub> heterocyclic ring; and
- the G junctions are both -CO- or -CONH.

2. Compounds as claimed in claim 1 in which the *linker* is selected from 1,3-cyclohexylene and 1,4-cyclohexylene.
3. Compounds as claimed in claim 1 or 2 in which the *linker* is selected from 1,2-, 1,3- or 1,4-phenylene.
4. Compounds as claimed in claim 1 in which the *linker* is selected from pyridyl, piperidiny, piperazinyl linked to the G<sub>1</sub> and G<sub>2</sub> groups in the positions 3,5 or 2,5 or 2,6.
5. The compounds of formula I for antitumour, antiarthritis, antiinflammatory and antiviral use.
6. Pharmaceutical compositions containing the compounds of formula I as active ingredients in admixture with suitable carriers and/or excipients.